Restriction/Election of Species Requirement

According to a new restriction/election requirement, the inventions listed as Groups I-XX on pages 3-7 of the Office Action "are not so linked as to form a single general inventive concept under PCT Rule 13.1." Therefore, Applicant was requested to elect one of the listed 20 inventions for examination purposes. Applicant was further requested to elect one of several patentably distinct species, if any of Groups I-XII, XIII, or XVII-XX were elected. This restriction/election requirement replaces the earlier restriction requirements of Paper Nos: 7 and 15, which have been vacated.

The invention of Group I, Claims 1-5, and 11, is hereby elected, *with traverse*. The elected method was originally drawn for treating or preventing cancer, comprising administering an agent having the property of disrupting the binding of human p53 and mdm2, wherein the agent comprises a peptide having a sequence corresponding to human p53, or a peptide having a motif FXaaaXaaaXaaaW (SEQ ID NO: 4), where Xaa is any amino acid. Applicants further elect the species of a peptide having a sequence corresponding to human p53, *also with traverse*. Due to current amendments to claim 1, the further requirement of electing either prevention or treatment is moot.

Applicant submits that the present restriction/election requirement contravenes the provisions of PCT Rules 13.1-13.3, and should be withdrawn. It is, again, emphasized that that PCT Rules 13.1-13.3 clearly allow the inclusion in one international application of claims that are linked as to form a single general inventive concept. The determination of whether the claims are so linked is to be carried out by assessing the contributions of each of the claimed inventions over the prior art.

All claims pending in the present application are unified by the feature that the methods are applied to cells in which mdm2 is not overexpressed. It is acknowledged

prior art that molecules that inhibit the binding of p53 to mdm2 have implications for the treatment of conditions in which mdm2 is overexpressed. This was based on the belief that, when overexpressed, mdm2 sequesters p53 and prevents it from carrying out its tumor suppressor role in inducing cell cycle arrest or apoptosis after DNA damage (see the "Background of the Invention" section of the present application).

The present invention is based on the surprising discovery that mdm2 binds to p53 and targets for destruction in a wider range of cells than previously thought, i.e. in cells in which mdm2 is not overexpressed. This is surprising, because previous reports had suggested that cell proliferation might depend on a fine balance between expression of mdm2 and p53 (specification, page 1, lines 17-21). This recognition is also of great practical importance, because only a subset of cancers overexpress mdm2.

The present invention therefore relates to a new application, to which the generally known methods of inhibiting the interaction of p53 and mdm2 may be put. By ignoring the fact that the claims are all limited to cells which do not overexpress mdm2, the Examiner has ignored the very feature that distinguishes the present invention from the prior art.

The election of species requirement is traversed on the ground that claim 5 is dependent on claim 3, so that the second "species" (a peptide having a motif FXaaXaaXaaW) carries all the limitations of the first one (a peptide having a sequence corresponding to human p53). In view of this, the two embodiments cannot be considered as different "species" at all.

Finally, it is noted that this is the third restriction requirement issued in connection with the present application, each being fully inconsistent with the previous one, which has resulted in unreasonable delays in the prosecution on the merits, and is contrary to the requirement of expeditious examination of patent applications.

It is submitted that the examination of all claims pending does not place an undue burden on the Examiner, therefore, the withdrawal of the present restriction/election requirement, in compliance with the PCT Rules, is respectfully requested.

Should the Examiner contemplate maintaining the present rejection, the Examiner is requested to contact the undersigned attorney to arrange an interview prior to issuance of a further Office Action.

Objections

Claims 4 and 3-5 were objected to for their recitation of the terms "corresponding" and "corresponding to," respectively. Since these terms are no longer present, the present objections are moot.

Rejection under 35 U.S.C. 112, first paragraph, written description

Claims 3-4 were rejected as allegedly containing subject matter "which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Specifically, the Examiner asserts that the specification does not disclose a representative number and range of peptides that will disrupt the interaction of p53 and mdm2, and takes the position that the claims should be limited to the peptides of SEQ ID NOs. 2 and 3, i.e. peptides having the amino acid sequences shown in Figure 1.

Applicant submits that it is "the invention" that must be sufficiently described, and that this rejection misses the point of the invention. The invention is based on finding a new class of situations in which one would want to disrupt the binding of p53 and mdm2. Known ways of doing so may be used. Both WO 93/20238 (e.g. Figures 6 and 7) and WO 96/02642 (e.g. Figures 3, 5 and 6) to which the present application refers extensively, disclose numerous peptides that are modeled on the mutual binding sites of p53 and mdm2 and that retain the ability to bind. These are expected to be capable of disrupting the interaction of p53 and mdm2. Accordingly, the Examiners assertion (page

12, 2nd and 4th lines from bottom) that "the general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed" is incorrect. The cited documents do indeed provide specific guidance.

Moreover, U.S. patents have been granted that are equivalent to WO 93/20238 and WO 96/02642. U.S. Patent No. 6,153,391 - which is equivalent to WO 96/02642 - includes claimed to methods that involve generically defined compounds (even including small molecules) that bind to MDM2 and interfere with its binding to p53. As an issued patent, U.S. Patent No. 6,153,391 (a copy of which is enclosed) has a presumption of validity, accordingly, its written description (and by analogy that of WO 96/02642) is presumed to meet the written description requirement of 35 U.S.C. §112, first paragraph for such generically defined compounds that are capable of interfering with the interaction of p53 and mdm2. By way of its reference to WO 96/02642, the present disclosure too must meet the same requirement.

The law is clear that it is the "*specification*" as a whole, and *not solely the working examples* that need to be examined in order to determine whether the written description provided is sufficient to support the invention as claimed. Indeed, as evidence of possession, an actual reduction to practice (such as a working example) is not always required, and what is conventional or known to one skilled in the are need not be described. It is submitted that proper application of this legal standard should result in the withdrawal of the present rejection.

Rejection under 35 U.S.C. §112, first paragraph, enablement, including scope

Claims 1-4, and 11 have been rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

In addition to reasons similar to those addressed in connection with the previous "written description" rejection, the rejection is based on the assertion that *in vitro* results cannot be extrapolated to the treatment of cancer *in vivo*. The claims have now been amended to avoid explicit reference to *in vivo* methods, thereby rendering the issue moot. Basis for the current amendments is at least at page 34, lines 3-13.

It is emphasized, however, that the present amendment is made without prejudice and without acquiescing to the rejection or the Examiner's reasoning underlying the rejection. Indeed, Applicant specifically retains the right to file one or more continuing applications to cover subject matter not specifically covered by the claims as currently amended.

As to the part of the present rejection that seems to relate to the scope of the claims rejected, Applicant refers to the arguments made in rebuttal of the "written description" requirement. While Applicant appreciates that the legal standard is different, the issuance of the enclosed U.S. Patent No. 6,153,391 also creates the presumption that the patent meets the statutory enablement requirement. The present disclosure, which provides an equivalent teaching should be accepted as enabling for the same reason. The Examiner's attention is directed to the discussion of the "invention" in the previous section. Since it is "the invention" that needs to be enabled, and also since it is a person skilled in the art (presumptively being aware of all relevant prior art) that need to be enabled to use the invention, the disclosure of the present application, in view of the state of the art at the effective filing date, is believed to satisfy the enablement requirement within the full scope of the claims pending.

Finally, the Examiner's remark that one cannot extrapolate from cancers that do not overexpress mdm2 to all cancers, seems to be based on a misunderstanding of the invention. Of course, Applicant is not claiming all cancers or cancer cells, only those that do not overexpress mdm2. This comes from the fact that claim 11 is dependent from claim 1.

In view of the foregoing arguments, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Rejection under 35 U.S.C. §102

Claim 11 has been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 96/02642A1.

In raising this rejection, the Examiner has overlooked the requirement in all claims that the methods are applied to cells that do not overexpress mdm2 in such cells. Rather, the rejection consistently (and erroneously) refers to overexpression of mdm2.

In particular, WO 96/02642 refers to WO 93/20238, and states:

> "This application . . . discloses that human MDM2 protein binds with human p53 and it has been suggested that molecules which inhibit the binding of MDM2 to p53 would be therapeutic by alleviating the sequestration of p53."

WO 96/02642 further develops the disclosure of WO 93/20238 and relates to the precise identification of the mdm2 binding site on p53.

However, both WO 96/02642 and WO 93/20238 consistently refer to gene amplification and overexpression of mdm2, as reflected, *inter alia*, by the following passages. In all cases, the emphasis is added.

WO 93/20238

Background, page 4, lines 8-14:

> "A gene, designated MDM2, which is amplified more than 50-fold in 3T3DM [a tumorigenic mouse cell line] cells, induced tumorigenicity when overexpressed in [mouse] NIH3T3 and Rat2 cells. From the nucleotide and predicted amino acid sequence of mouse MDM2 (mMDM2), Fakharzadeh speculated that this gene encodes a potential DNA binding protein that functions in the modulation of expression of other genes and, when present in excess, interferes with normal constraints on cell growth."

Summary of the invention, page 5,lines 11-17:

"It has now been discovered that hMDM2, a heretofore unknown human gene, plays a role in human cancer. The hMDM2 gene has been cloned and the recombinant derived hMDM2 protein shown to bind to human p53 *in vitro*. hMDM2 has been found to be amplified in some neoplastic cells and the expression of hDND2-encoded products has been found to be correspondingly elevated in tumors with amplification of this gene. The elevated levels of MDM2 appear to sequester p53 and allow the cell to escape from p53-regulated growth.

Detailed description of the invention, page 7, line 22 to page 8, line 5:

"It is a discovery of the present invention that a gene exists which is amplified in some human tumors. The amplification of this gene, designated MDM2, is diagnostic of neoplasia or the potential therefor. Detecting the elevated expression of human MDM2-encoded products is also diagnostic of neoplasia or the potential for neoplastic transformation. Over a third of sarcomas surveyed, including the most common bone and soft tissue forms, were found to have amplified hMDM2 sequences. Expression of hMDM2 was found to be correspondingly elevated in tumors with the gene amplification.

Other genetic alterations leading to elevated hMDM2 expression may be involved in tumorigenesis also, such as mutations in regulatory regions of the gene. Elevated expression of hMDM2 may also be involved in tumors other than sarcomas . . . "

Page 9, lines 1-11:

"The term elevated expression means an increase in mRNA production or protein production over that which is normally produced by non-cancerous cells. Although amplification has been observed in human sarcomas, other genetic alterations leading to elevated expression in MDM2 may be present in these or other tumors. . . . Non-cancerous cells for use in determining base-line expression levels can be obtained from cells surrounding a tumor, from other humans or from human cell lines. Any increase can have diagnostic value . . .

WO 96/02642

Page 3, lines 13-18:

"Up to a third of human sarcomas are considered to overcome p53-regulated growth control by amplification of the *mdm2* gene."

Page 12, line 35 to page 13, line 4:

"Hence the invention provides a method for inhibiting the growth of tumour cells which contains a human MDM2 gene amplification, the method comprising applying to said tumor cells a DNA molecule which expresses a polypeptide [containing the MDM2 binding site of p53]."

In the absence of any reference to cells in which mdm2 is not overexpressed, the claims of the present application are not anticipated by the cited reference, and the present rejection should be withdrawn.

Sequence Rule Compliance

In the foregoing amendment to the specification, the figure legend to Figures 1 has been supplemented by sequence identifiers. Therefore, the present objection is believed to be moot.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney

Docket No.: 39749-0001APC). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Dated: September 30, 2003

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